High incidence and prevalence of multiple sclerosis in south east Scotland: evidence of a genetic predisposition

P M Rothwell, D Charlton

Abstract

***Objective*—To determine the incidence and prevalence of multiple sclerosis in the Lothian and Border Health Board Regions of south east Scotland.**

***Methods*—Incidence study: all patients were identified in whom a diagnosis of Poser category probable or definite multiple sclerosis was made by a neurologist between 1992 and 1995. Prevalence study: all patients known to have multiple sclerosis who were alive and resident in the study area on 15 March 1995 were recorded.**

***Results*—The crude annual incidence rates of probable or definite multiple sclerosis per 100 000 population were the highest ever reported: 12.2 (95% confidence interval (95% CI) 10.8–13.7) in the Lothian Region and 10.1 (95% CI 6.6–13.6) in the Border Region. A total of 1613 patients with multiple sclerosis were resident in the study area, giving standardised prevalence rates per 100 000 population of 203 (95% CI 192–214) in the Lothian Region and 219 (95% CI 191–251) in the Border Region. Prevalent cases were more likely than expected to have a Scottish surname (risk ratio 1.24, 95% CI 1.14–1.34).**

***Conclusions*—Orkney and Shetland were previously thought to have by far the highest prevalence of multiple sclerosis in the world: about double that found in England and Wales. However, the prevalence in south east Scotland is equally high, suggesting that the Scottish population as a whole has a genetic susceptibility to the disease, and undermining the hypothesis that patterns of infection specific to small sparsely populated island communities are important in the causation of multiple sclerosis.**

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There is considerable variation in the prevalence of multiple sclerosis around the world.[1] The geographical distribution has been studied in the hope that, along with the results of genetic epidemiology and migration studies, it might provide clues to the aetiology of the disease. The prevalence of multiple sclerosis increases with latitude north and south of the equator. This could be due to differential exposure to a causative environmental agent,[2] although none has been identified. Alternatively, it has been pointed out that the prevalence of multiple sclerosis is highest in those countries with a high proportion of people of Scottish or Scandinavian ancestry,[3] the latitudinal gradient partly reflecting differences in genetic susceptibility. Similar correlations between the frequency of northern European ancestry and a latitudinal gradient in the prevalence of multiple sclerosis have also been shown within North America[4] and New Zealand,[5] although there was no such correlation to account for the threefold variation in prevalence with latitude in Australia.[6]

Scotland has the highest prevalence of multiple sclerosis in the world.[7 8] The prevalence rates reported in Orkney and Shetland are about double the highest rates reported in other parts of northern Europe.[8–10] This may be due to genetic susceptibility or to the unusual pattern of environmental exposures, particularly infections, in small sparsely populated island communities. The apparent occurrence of epidemics of multiple sclerosis on other similar island communities, such as the Faroe Islands, is often quoted in support of this explanation.[11] However, the existence of a latitudinal gradient in the prevalence of multiple sclerosis in the United Kingdom is now being questioned.[12–18] Recent studies in England and Wales have reported the prevalence of multiple sclerosis to be higher than was previously thought,[12–17] and it has been argued that the prevalence rates in Orkney and Shetland are unreliable because they were the result of repeated surveys of the same areas over many years, they were based on very few cases, and they used different diagnostic criteria. More up to date and reliable information on the prevalence of multiple sclerosis in a previously unsurveyed area of Scotland is required to determine whether or not the disease does cluster in Orkney and Shetland or whether there is a high incidence throughout Scotland.

We determined the incidence and prevalence of multiple sclerosis in the Lothian and Border Regions of south east Scotland, and examined the relation between possession of a Scottish surname and the risk of developing multiple sclerosis. We also related regional variations in the prevalence of surnames with the prefix "Mc" or "Mac", indicating Scottish ancestry, to the prevalence of multiple sclerosis in various parts of the United Kingdom.

Table 1 Poser categorisation[19] of incident cases of multiple sclerosis (MS) in Lothian and Border regions in the pilot study and the prospective incidence study

Poser category	*Pilot study (1989–92)*	*Prospective study (1992–95)*
Clinically definite MS	102	132
Laboratory supported definite MS	73	67
Clinically probably MS	58	110
Laboratory supported probable MS	3	1
Subtotal	236	310*
Incidence/100 000/year	9.3	12.0
Possible MS	108	160
Total	344	470

*278 in Lothian Region and 32 in Border Region

Methods

PILOT STUDY

To estimate the likely prevalence of multiple sclerosis in south east Scotland and therefore determine the study population sample size necessary to have sufficient statistical power to test our hypothesis that the prevalence was higher than that in recent studies in southern England, we performed a retrospective study of the incidence of multiple sclerosis in the Lothian and Border Regions between 1989 and 1992. All outpatient clinic letters and inpatient discharge summaries from the Department of Neurology in Edinburgh and peripheral neurology clinics in five general hospitals serving the study area were screened. We identified 344 patients in whom a new diagnosis of Poser category[19] probable or definite multiple sclerosis had been made by a neurologist between 1989 and 1992 and who were resident in the study area. The crude hospital based incidence was calculated to be 9.3/100 0000/year. On the basis of the incidence:prevalence ratios in other recent studies,[12 15–17] we estimated the expected prevalence of multiple sclerosis in the study area to be about 200/100 000.

SAMPLE SIZE

Assuming a prevalence of 200/100 000, we calculated that a study population denominator in excess of 500 000 would be required to show a statistically significant difference at the 99% level of confidence from the prevalences reported in recent studies in the south of England. It was therefore decided to perform the formal prevalence study on the whole of Lothian and Border Regions. The projected number of prevalent cases in this study region was about 1700. The study would therefore be considerably larger than previous prevalence studies in the United Kingdom, and it was not considered feasible for all suspected prevalent patients to be interviewed and examined by a study neurologist. However, to test the validity of the prevalence figure, a prospective study of the incidence of multiple sclerosis in the study region was performed from 1992 to 1995. Only patients in whom a new diagnosis of multiple sclerosis had been made by a neurologist were included. Approval for the studies was obtained from the local ethics committee and the studies complied with the Data Protection Act.

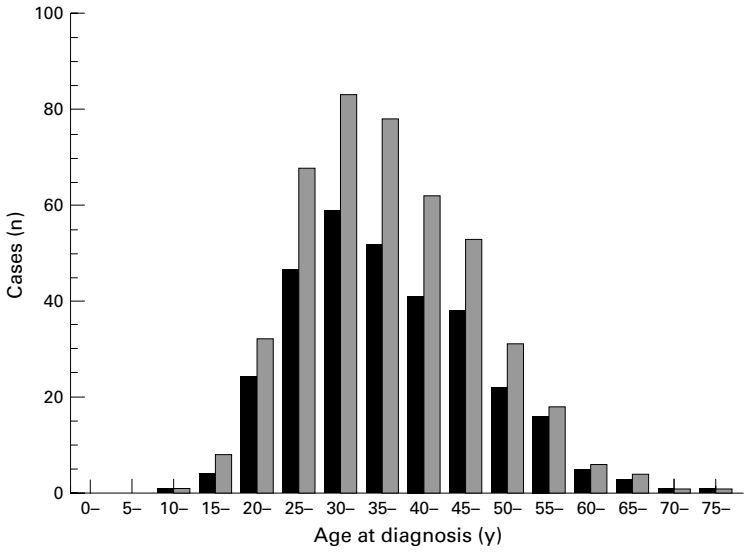

Figure 1 Age at diagnosis of incident cases of multiple sclerosis in the combined study region from 1992–5. The solid bars represent cases of Poser category probable and definite multiple sclerosis and the hatched bars include possible cases.[19]

STUDY AREA

Lothian and Border Regions are the two adjacent health board regions of south east Scotland. Their combined area lies between latitudes 55 30' and 56 00' north. The midyear population estimate for 1995 was 864 300 (105 700 in the Borders Region). The area is served by 604 general practitioners (79 in the Borders Region), five general hospitals (one in the Borders Region), and a single department of neurology located at two hospitals in Edinburgh.

PROSPECTIVE INCIDENCE STUDY

The study was limited to cases in which a new diagnosis of multiple sclerosis was made by a neurologist from 1 January 1992 to 31 December 1995. Cases were ascertained from the neurology and neurosurgery wards and all outpatient clinics in the Department of Neurology in Edinburgh and peripheral neurology clinics in the five general hospitals in the study area. Possible cases were also identified from requests and reports of MRI of the brain or spinal cord, visual and somatosensory evoked potential studies, and CSF oligoclonal bands. Full details of clinical presentation and investigations were obtained from the medical records of all suspected cases allowing a Poser category[19] to be allocated. However, as in previous studies,[12 16] the upper limit of 59 years for age at presentation used in the Poser categorisation was ignored.

PREVALENCE STUDY

A prevalent case was defined as any person with a diagnosis of multiple sclerosis who was alive and normally resident in the Lothian or Border regions on 15 March 1995. Cases with a Poser category of probable or definite multiple sclerosis identified from neurological records in the pilot study and the prospective incidence study were included in the prevalence figure. All prevalent cases of Poser category probable or definite multiple sclerosis who were seen in the Department of Neurology or in peripheral neurology clinics in the five hospitals in the study area between 1989 and 1995 were also identified from discharge

Table 2 Sources of identification of the 1613 prevalent cases of multiple sclerosis in the combined Borders and Lothian study region

Source	Means of initial identification n (%)	Diagnosis not assessed by review of medical or neurology records n (%)
Department of neurology records	1008 (62)	
Hospital discharge diagnostic coding	455 (28)	69 (4)
General practitioner	881 (55)	271 (17)
Neurorehabilitation unit records	40 (3)	22 (1)
Disability services records	73 (5)	46 (3)

summaries, clinic letters, and review of medical records. Letters were sent to all general practitioners in the study area requesting the name, date of birth, and address of all patients on their lists with a firm diagnosis of multiple sclerosis. No specific diagnostic criteria were suggested. Lists of all patients with a diagnosis of multiple sclerosis discharged from each of the five hospitals in the region between 1990 and 1995 were obtained using computerised discharge diagnostic coding data. Other sources of cases included the records of the local neurorehabitation hospital and the disability and wheelchair services unit in the study region. Information on cases resident in nursing homes was requested from general practitioners. Information from local multiple sclerosis charities was not used because their records did not specify which of their members had a diagnosis of multiple sclerosis. The Social Services Disability Register also had insufficient diagnostic information. An attempt was made to trace the medical and neurology records of all cases identified who had not already been identified during our review of department records of 1989–95. General practitioner records were not reviewed. Whether cases were still alive and resident in the study area on the prevalence date was checked using the general practitioner registration computer databases in the two study areas.

STATISTICAL ANALYSIS

As in most previous studies, the prevalence rates were standardised to the 1961 census population of Northern Ireland.[20] Ninety five per cent confidence intervals (95% CIs) were calculated on the assumption of a Poisson distribution.[21]

RISK ASSOCIATED WITH A SCOTTISH SURNAME

Using a standard text,[22] and blind to sex and Christian names, prevalent cases with surnames which are considered to have originated in Scotland were identified. The proportion of prevalent cases with Scottish surnames was compared with that expected on the basis of the surname frequencies in the general population in the study region. The sex ratio of cases with Scottish surnames was compared with that of cases with non-Scottish surnames.

THE GEOGRAPHICAL DISTRIBUTION OF SURNAMES WITH THE PREFIX MC/MAC

The prefix Mc or Mac, meaning "son of", came into use in Scotland in the 13th century, and can be used as a crude surrogate of Scottish ancestry. The proportion of people with surnames beginning with the prefix Mc or Mac, measured to the nearest centimetre of column length, was obtained by hand for the 104 British Telecom phone books covering England, Scotland, and Wales in 1994.

Results

For the purposes of the pilot study, the prospective incidence study, and the prevalence study the records of over 75 000 neurology outpatient consultations and inpatient admissions between 1989 and 1995 were reviewed. Table 1 shows the Poser categorisation of the 344 retrospectively identified incident cases from the pilot study.

PROSPECTIVE INCIDENCE STUDY

A total of 549 incident cases of possible multiple sclerosis were identified between 1992 and 1995. Review of case notes disclosed that 68 were subsequently found to have another diagnosis. Of the 481 cases which remained, 160 were categorised as only "possible" multiple sclerosis according to the Poser criteria, and insufficient information was available to categorise the patient in 11 cases. The remaining 310 cases had a Poser category of "probable" or "definite" multiple sclerosis (table 1). These comprised 216 females and 94 males (ratio = 2.30, 95% CI 2.00–2.63). The median age at diagnosis was 34 years (range 8–75 years, fig 1). The crude annual incidence per 100 000 population was 12.2 (95% CI 10.8–13.7) in Lothian region, 10.1 (95% CI 6.6–13.6) in the Border Region, and 12.0 (10.6–13.3) in the combined study region (table 1). If Poser category possible cases are included, the incidence figure for the combined area rises to 18.1 (95% CI 16.5–19.8).

PREVALENCE STUDY

In addition to the incident cases detailed above, 462 cases of probable or definite

Table 3 The prevalence of multiple sclerosis in the combined Lothian and Border study region per 100 000 by age and sex

Age (y)	Male n	Male Rate/10^5	Male (95% CI)	Female n	Female Rate/10^5	Female (95% CI)	Total n	Total Rate/10^5	Total (95% CI)
0–4	1	1	(0–4)	3	4	(0–9)	4	3	(1–5)
14–24	8	13	(4–21)	14	24	(11–36)	22	18	(11–26)
25–34	53	70	(52–89)	153	209	(176–242)	206	139	(120–158)
35–44	121	203	(167–239)	281	467	(413–522)	402	336	(303–369)
45–54	110	214	(174–254)	312	584	(519–648)	422	403	(364–441)
55–64	108	263	(214–313)	185	408	(349–467)	293	339	(300–378)
65–74	51	153	(111–195)	147	346	(290–402)	198	261	(225–298)
>75	41	78	(37–119)	43	115	(81–150)	57	103	(77–130)
Unknown	2			7			9		
Total	468	112	(102–122)	1145	257	(242–272)	1613	187	(178–196)

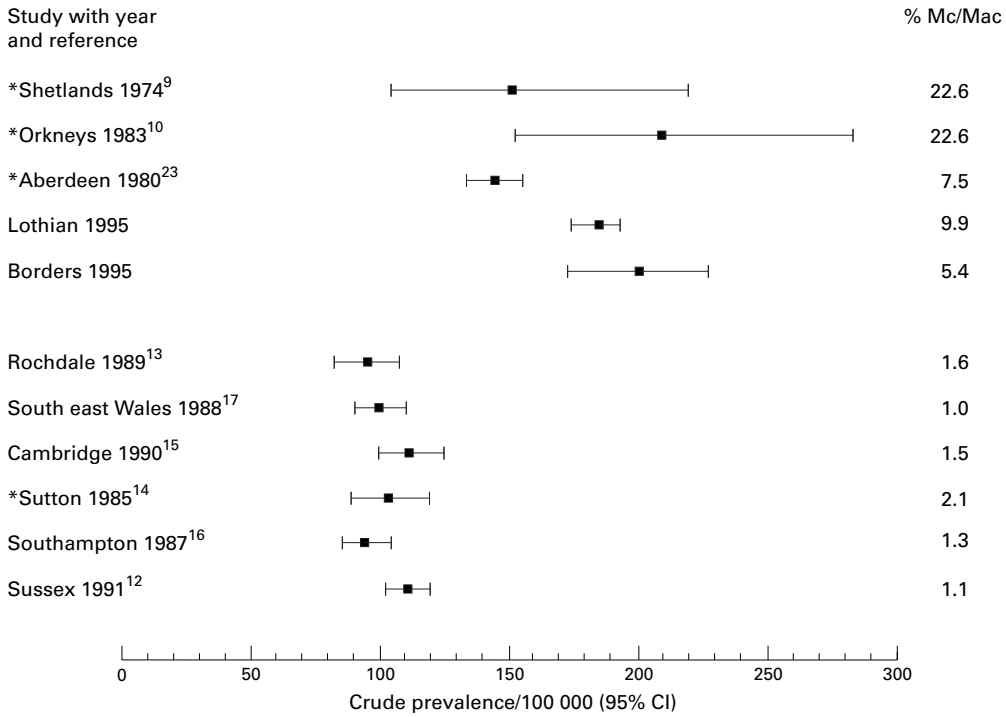

*Figure 2 A comparison of the crude prevalence rates for multiple sclerosis in the most recent studies in Scotland, England, and Wales. Where available the figures quoted are based on the Poser category probable and definite cases. For those studies in which these data are unavailable (marked with *) the figures are based on the Allison and Millar criteria,[27] excluding possible cases. The proportion of the population in each of the study areas with surnames including the prefix Mc or /Mac (based on 1994 data) are given on the right.*

multiple sclerosis already prevalent on 1 January 1989 were identified from the initial review of inpatient and outpatient neurology records. A diagnosis of probable or definite multiple sclerosis was confirmed from medical and neurology records in a further 197 cases notified from other sources, leaving 408 (25%) cases in which no hospital records were available. Most of these cases (271) were notified by general practitioners (table 2).

Notifications of cases were received from 92% of general practices in the study region. Notification by general practitioner was the sole initial source of information on 397 (25%) cases. However, the diagnosis was subsequently confirmed from the case records in 126 of these, leaving 271 (17%) cases in which no other evidence was available. Of the 268 patients who had been seen in the Department of Neurology between 1989 and 1995 and had had a Poser categorisation of only possible multiple sclerosis at their last attendance, only nine (3%) were notified by general practitioner as having a firm diagnosis of multiple sclerosis.

The provisional list of cases of multiple sclerosis reached 1793. Of these, 180 had died or were no longer resident in the study region on 15 March 1995. A total of 1613 patients with multiple sclerosis were resident in the study region on 15 March 1995 (1401 in the Lothian Region and 212 in the Border Region). The crude prevalence rates were 185 (95% CI 175–194) in the Lothian Region, 201 (95% CI 174–228) in the Border Region, and 187 (95% CI 178–196) in the combined region. The prevalence rates, standardised to the 1961 population of Northern Island, were 203 (95% CI 192–214) for the Lothian Region and 219 (95% CI 191–251) for the Border Region. The sex ratio was 2.45 (95% CI 2.31–2.59, 1145 female, 468 male), and the mean age of prevalent cases was 49.2 (SD 13.8) years, range 8–91, table 3).

SCOTTISH SURNAMES

Of the 1613 prevalent cases, 589 (37%) had surnames which are regarded as having their origins in Scotland compared with 476 expected on the basis of the frequency of Scottish names in the general population in the study region (RR 1.24, 95% CI 1.14–1.34). Prevalent cases with Scottish surnames were more likely to be male than those with non-Scottish surnames (M:F = 194:395 *v* 274:750, OR 1.34, 95% CI 1.08–1.68).

THE GEOGRAPHICAL DISTRIBUTION OF SURNAMES WITH THE PREFIX MC OR MAC

The proportion of names beginning with Mc or Mac was 1–2% throughout England and Wales with little latitudinal gradient (Regions: south west 1.1%; south east 1.2%; Greater London 1.8%; East Anglia 1.0%; south Midlands 1.5%; Midlands 1.2%; north east 1.8%; north west 1.9%; Wales 1.0%). The proportion increased sharply in Scotland (south 13.2%; north 9.4%; the Highlands and islands 22.6%). Figure 2 shows the proportion of the population in the study area of each of the recent prevalent studies in England, Scotland, and Wales.

Discussion

The incidence of multiple sclerosis in south east Scotland is the highest ever reported and the prevalence is about double those found in

recent studies in England and Wales.[12–17] Our data support the findings of older prevalence studies in Orkney,[9 10] Shetland,[9 10] and Aberdeen,[23] and suggest that there is no latitudinal gradient in the prevalence of multiple sclerosis within Scotland. Our study population was large, and the confidence intervals of the incidence and prevalence rates are narrow. By contrast, the high prevalences of multiple sclerosis in Orkney and Shetland were based on small numbers of cases with relatively small population denominators. For example, the highest crude prevalence of multiple sclerosis ever reported, 257/100 000 on Orkney in 1974,[10] using the Allison and Miller criteria, was based on 45 probable and early cases among a population of 17 462 and consequently had a wide 95% CI (192–344).

THE VALIDITY OF THE PREVALENCE FIGURE

By contrast with some of the recent studies in England and Wales,[15–17] we did not review the medical records, or interview or examine all our prevalent cases. It could be argued, therefore, that our high prevalence figures might be due partly to false positive diagnoses. However, there were no differences in the prevalence rates reported in England and Wales between studies in which the diagnosis was reviewed in all patients[15–17] and studies in which the methods were similar to ours.[12–14] The prevalence rates were, in fact, remarkably consistent (fig 2).

About 75% of our cases had the diagnosis of probable or definite multiple sclerosis confirmed from their medical or neurology records. Although 17% of our cases were notified solely by their general practitioner, and no medical or neurology records were available, most of these cases are likely to have been seen and investigated by a neurologist at some time in the past. The median age of such cases in our study was 52 years compared with a median age of diagnosis of 34 years in our incident cases. The cases notified solely by general practitioners would, on average, therefore have been diagnosed nearly 20 years before our study, and would not be expected to be attending hospital on a regular basis. The fact that as many as 60% of our prevalent cases had attended the neurology services during the six years before our prevalence date suggests that we are actually more likely to have underestimated the true prevalence of the disease in the community.

That general practitioners were not overdiagnosing multiple sclerosis is shown by the fact that only nine (3%) of the 268 patients who had been seen in the department of neurology over the previous six years with a neurological episode that was thought possibly to have been an early manifestation of multiple sclerosis (Poser category: possible) were notified by their general practitioner as having a firm diagnosis.

THE INCIDENCE OF MULTIPLE SCLEROSIS

By contrast with the prevalent cases, all of the incident cases in our study had been investigated and diagnosed by a neurologist. Using their neurology records we were able to assign a Poser category based on the evidence available at last review. The incidence rate cannot, therefore, be regarded as an overestimate. In fact, since we may well have missed some of the cases which were investigated by general physicians and not referred to the Department of Neurology, we may have underestimated the true incidence of the disease. The reported incidences of multiple sclerosis in studies in England and Wales which have used the Poser criteria have been consistently in the region of 5/100 000/year.[12 15–17] The incidence rate in our study area is the highest ever reported and provides strong support for the validity of the high prevalence rate. In fact, the crude prevalence:incidence ratio of 15.6 is lower than that in previous studies: 22.2[12]; 20.5[15]; 24.5[16]; and 25.7.[17]

THE ROLE OF SCOTTISH ANCESTRY

Although the prevalence of multiple sclerosis is considerably higher in Scotland than in England or Wales, there is no evidence from prevalence studies,[12–17] general practice diagnostic databases,[24] mortality data,[7] or hospital discharge data[7] that there is any latitudinal gradient within England or Wales. It would seem, therefore, that the prevalence of multiple sclerosis increases fairly sharply at the border of England and Scotland and then remains relatively constant with increasing latitude within Scotland.[25] This is difficult to explain in terms of an environmental risk factor. Rather it suggests a difference in the genetic susceptibility of the respective populations.

The higher than expected proportion of cases of multiple sclerosis with Scottish surnames in our study is consistent with the hypothesis that Scottish ancestry is associated with an increased susceptibility to multiple sclerosis. Furthermore, although a relatively crude measure of Celtic ancestry, the sharp increase in the proportion of surnames prefixed with Mc or Mac at the Scottish border does suggest that, whereas there must clearly have been considerable population mixing over the centuries, the populations of England and Scotland do still have substantially different ancestry. In keeping with this, the HLA allele DR2, which is associated with susceptibility to multiple sclerosis, is twice as prevalent in Scotland as in England.[7] The high prevalence of multiple sclerosis in the South Island of New Zealand has also been related to a high frequency surnames prefixed with Mc or Mac.[26] It should be noted, however, that the increase in the proportion of surnames prefixed with Mc or Mac with latitude within Scotland is not associated with an increase in the prevalence of multiple sclerosis.

In conclusion, the incidence of multiple sclerosis in south east Scotland between 1992 and 1995 was the highest ever reported, and the prevalence was about double that reported in England and Wales and similar to that in Orkney and Shetland. The very high prevalences of multiple sclerosis found in Orkney and Shetland are unlikely therefore to be due to peculiarities of the small island environments and are more likely to be due to a genetic predisposition to the

disease. Scottish ancestry appears to be a "risk factor" for the development of multiple sclerosis, and this may explain the high prevalence of the disease in countries in which there are significant numbers of Scottish migrants.

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